Alcohol and the Immune System

One of the least appreciated medical complications of alcohol abuse is its effect on the immune system. Excess alcohol consumption may lead to immune deficiency, causing increased susceptibility to certain diseases. Life-threatening complications of alcoholism such as liver disease and liver failure may have a component of autoimmunity, in which the immune system turns on the body's own tissues. This section describes current research that is providing new insights into the regulation of the immune system in people who drink alcohol heavily by examining alcohol-related alterations in the cells and molecules that shape the immune response. It also describes some of the exciting new techniques that are being designed to improve or restore immune function by manipulation of these cells and molecules. Although much remains to be learned, researchers are making rapid progress in understanding alcohol-related immune disorders.

Alcohol and Diseases Related to the Immune System

Physicians have long observed that excessive alcohol consumption can lead not only to liver damage but also to increased illness and death from infectious diseases such as pneumonia. (See, for example, the writings of Philadelphia physician Benjamin Rush [1745–1813] [Rush 1943]). We now regard this increase in disease as the result of immunodeficiency caused by alcohol abuse. Further, there is reason to suspect that the organ damage, such as alcoholic liver disease, observed in people who drink alcohol heavily is at least partially caused by alcohol-triggered autoimmunity in which the immune system attacks the body's own tissues. A number of reviews in the literature provide an overview of current knowledge concerning alcohol's effects on the human immune system (Baker and Jerrells 1993; Cook 1995, 1998; Frank and Raicht 1985; Ishak et al. 1991; Johnson and Williams 1986; Kanagasundaram and Leevy 1981; MacGregor and Louria 1997; Mendenhall et al. 1984; Mufti

et al. 1989; Palmer 1989; Paronetto 1993; Watson et al. 1986).

Diseases Related to Immunodeficiency

Pneumonia

In the early part of this century, researchers noted that alcoholics were more than twice as likely as nonalcoholics to die from pneumonia (Capps and Coleman 1923). Despite the availability of antibiotics in the modern era, alcohol abusers still suffer from increased susceptibility to bacterial pneumonia (Chen et al. 1992; Chomet and Gach 1967; Cortese et al. 1992; Esposito 1984; Kuikka et al. 1992; Kuo et al. 1991). Further, a study of all patients with pneumonia has shown that a high percentage were alcohol abusers, even though they may not have been diagnosed previously as alcoholics (MacGregor and Louria 1997). Clearly, the effects of alcohol abuse on illness rates and treatment costs for pneumonia are considerable.

Tuberculosis

The incidence and severity of pulmonary tuberculosis (TB) is greater in alcoholics than in nonalcoholics (MacGregor and Louria 1997). In the overall population, 16 percent of TB patients are alcohol abusers; the percentage ranges up to more than 35 percent in some populations (Centers for Disease Control and Prevention [CDC] 1996). For example, long-term studies of drug and alcohol abusers who were followed for many years showed that these individuals had TB incidence rates from 15 to 200 times the rates for control populations (Friedman et al. 1987, 1996). In recent years, the incidence of TB has been increased by the presence of human immunodeficiency virus (HIV) in drug and alcohol abusers. However, even after this added risk is taken into account, it is still clear that drug and alcohol abusers have increased rates of illness and death from TB (CDC 1996; White and

Portillo 1996). The recent rise of drug-resistant strains of the TB bacillus (CDC 1996) gives even greater urgency to the need for effective intervention among populations at risk of TB, both nationally and worldwide.

HIV

Infection with HIV, which leads in its later stages to acquired immunodeficiency syndrome (AIDS), has become one of the great epidemics of our time, with millions infected worldwide. Transmission is primarily through sexual contact or the sharing of used needles by drug abusers. Alcohol abusers may be at increased risk for infection due to risky sex practices compared with nonabusers (MacGregor and Louria 1997), but two questions remain unanswered. The first question is whether alcohol consumption, either before or at the time of exposure, increases susceptibility to infection. The second question is whether alcohol use hastens the progression from asymptomatic HIV infection to full-blown AIDS. Studies of alcohol effects on HIV using isolated white blood cells have produced conflicting results. One research group reported an increased HIV growth rate after prior alcohol consumption by donors of the cells (Bagasra et al. 1989, 1993, 1996). A second group found no consistent effect (Cook et al. 1997*b*). A recent clinical study of HIV-positive drug abusers who were followed for several years showed that those who drank alcohol heavily had significantly more abnormalities in the T-lymphocytes (T-cells; see the discussion in this section on the immune system) than did those who were light alcohol drinkers or abstainers (Crum et al. 1996). Since both HIV-infected individuals and noninfected alcohol abusers have compromised immune systems, the question of interactions between these two conditions remains important for investigation.

Hepatitis C and Hepatitis B

Many recent studies have attempted to determine the relationship between alcohol abuse and hepatitis C virus (HCV) or hepatitis B virus (HBV) infection. The most recent studies have determined that, after correction for nonalcohol-related risk factors such as intravenous drug abuse and unsafe sexual practices, alcoholics do not have an increased incidence of HBV but do have an increased HCV incidence of about 10 percent compared with nonalcoholics (Rosman et al. 1996). If alcoholics are considered as a group without excluding other risk factors for infection, the prevalence of either HBV or HCV is in the range of 10 to 50 percent (French 1996; Grellier and Dusheiko 1997; Rosman et al. 1996). These hepatitis-positive patients are suffering from two diseases, alcoholism and nonalcoholic viral hepatitis, that may have additive or synergistic effects on the development of liver disease. Both conditions may affect the immune system to produce immunodeficiency and autoimmunity.

Other Infections

Alcohol abusers are more susceptible than non-abusers to other infections, such as septicemia, which is an infections of the circulating blood. In some cases, septicemia is caused by bacterial spread from pneumonia. Other infections that may lead to septicemia in the alcohol abuser include urinary tract infections and bacterial peritonitis, an infection of the lining of the abdominal cavity (Chen et al. 1992; Cortese et al. 1992; Esposito 1984; Kuikka et al. 1992; Kuo et al. 1991).

Alcoholics appear to be more susceptible than nonalcoholics to several less common infections, such as lung abscess, empyema (an accumulation of pus in the chest), spontaneous bacterial peritonitis, diphtheria, cellulitis (an inflammation of connective tissue), and meningitis (an inflammation of the membranes of the brain and spinal cord) (MacGregor and Louria 1997). It is clear that the increased incidence of infectious diseases in alcohol abusers represents a significant toll of individual suffering and of medical expense to society.

Diseases Related to Autoimmunity

A disastrous medical complication of chronic alcohol abuse is alcoholic liver disease with eventual liver failure. Alcoholic liver disease,

which includes alcoholic hepatitis, cirrhosis, and fatty liver, is discussed in the section "Alcohol-Induced Liver Injury" earlier in this chapter and in the *Ninth Special Report to the U.S. Congress on Alcohol and Health* (National Institute on Alcohol Abuse and Alcoholism 1997). Several extensive reviews present an overview of published research (Lieber 1994; Mendenhall et al. 1984, 1995).

Alcoholic hepatitis is characterized by acute liver inflammation and cell death. In severe cases, death of the patient occurs in one to several weeks after admission to the hospital. There is evidence that the immune system may cause some of the injury. One indication is that alcoholic hepatitis continues to worsen after withdrawal from alcohol, suggesting that the damage is not due solely to the presence of alcohol. A second indication of immune system involvement is that alcoholics who recover from alcoholic hepatitis but then resume drinking alcohol typically suffer new episodes of hepatitis. These recurrent episodes are more severe and occur at a lower level of alcohol consumption. This suggests a possible autoimmune process in which immunity to some component of the patient's own liver has developed and is exacerbated by a resumption of alcohol drinking.

In alcoholic cirrhosis, the structure of the liver is distorted by scarring due to the deposition of fibrous tissue, and the functional units of the liver—the lobules—are damaged. Eventually, this process may result in liver failure and death. Many cirrhosis patients also suffer from alcoholic hepatitis and may have autoantibodies against the liver, which would contribute to cell damage and scarring. Involvement of the immune system in alcoholic cirrhosis is currently under study.

Several other conditions with probable autoimmune origin have been noted in alcohol abusers. Kidney disease is increased in alcohol-abusing individuals in some racial groups or isolated populations, suggesting a possible genetic component (Smith et al. 1993). The presence of autoantibodies in a wide range of tissues in alcohol abusers supports the possibility that other illnesses in the alcoholic are of autoimmune

origin. Possible involved molecules include white blood cells, brain cells, deoxyribonucleic acid (DNA), and various proteins (Cook et al. 1996; Laskin et al. 1990; Paronetto 1993; Wehr et al. 1993).

The Immune System

The effects of alcohol on the immune system involve various types of immune cells and their interactions. These interactions are partly mediated by cytokines, chemical messengers that are described in some detail in the previous section, "Alcohol-Induced Liver Injury." The following discussion provides some background on the immune system and its components.

Two broad categories of immune cells are phagocytes and lymphocytes. Phagocytes are white blood cells that act by engulfing and destroying bacteria and other foreign substances. They include monocytes, neutrophils, and macrophages. Monocytes may circulate in the blood, or they may migrate into the tissues where they develop into fixed macrophages, such as the Kupffer cells in the liver. Neutrophils circulate in the blood and are among the first cells to arrive at the site of an injury or infection.

Lymphocytes are white blood cells produced in the lymphoid organs, mainly the bone marrow, thymus, lymph nodes, and spleen. Two of the main types of lymphocytes are T-cells, which are produced in the thymus, and B-lymphocytes (B-cells), which are produced in the bone marrow. There are several subtypes of T-cells. Helper T-cells respond to infection by secreting cytokines that stimulate other immune system cells. Cytotoxic T-cells recognize foreign substances, or antigens, on the surface of infected or transplanted cells and act by destroying these cells. Suppressor T-cells alter other immune responses in order to prevent overreaction of the immune system.

The B-cells are stimulated by antigens to produce antibodies, or immunoglobulins. Each B-cell is specific to one particular antigen. Most activated B-cells develop into plasma cells, which secrete

large numbers of antibodies into the blood stream. Specialized B-cells are the memory cells, long-lived cells that continue to circulate in the blood. If memory cells are re-exposed to the original antigen, they respond even more vigorously than in the initial response.

Another type of lymphocyte, the natural killer (NK) cell, provides an important defense against cancer and viral infections. NK cells can recognize, bind directly to, and destroy cells infected by viruses and, possibly, cancerous cells. They do not require previous exposure in order to recognize target cells.

Immune responses may be broadly classified as either cell mediated or humoral. Cell-mediated immunity refers to direct cell-to-cell immune response, such as that provided by the phagocytes and T-cells. Humoral immunity is provided by antibodies that circulate in the blood and lymph. The term refers to the body's fluids, or "humors." B-cells are the source of humoral immunity. T-cells play a central regulatory role, inhibiting or stimulating production of antibodies by B-cells, producing many different cytokines, interacting with monocytes, and interacting with and regulating other subclasses of T-cells. Monocytes interact with T-cells by presenting antigen to the T-cells, which leads either to stimulation of the production of antibody by B-cells or to cell-mediated responses by the T-cells themselves.

One of the most important developments in immunology in recent years has been the discovery of a vast network of regulatory molecules called cytokines. Many different types of these protein molecules are secreted by cells of the immune system, and changes in their balance have profound effects on the function of the immune cells. Some cytokines induce inflammation, including interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α, or TNF). Interleukin-10 (IL-10), on the other hand, has antiinflammatory effects. Interleukin-8 (IL-8) attracts neutrophils to the site of an infection. Interleukin-12 (IL-12) activates NK and helper T-cells and induces the cell-mediated immune response.

Changes in the Immune System of Alcoholics

Alcoholics often have greatly increased blood levels of immunoglobulins (Cook et al. 1996; Sheron 1994). The major classes of these antibodies are immunoglobulins A, G, and M (IgA, IgG, and IgM), each of which has a specialized role in the immune response. Typically, IgA is elevated in the blood of alcoholics both with and without alcoholic liver disease, while IgG is elevated in those with liver disease. IgM is elevated only in patients with active liver disease, such as alcoholic hepatitis. IgA also may be found as tissue deposits in the skin, liver, and kidney of alcoholics (Paronetto 1993). Although an increase in a given antibody is usually associated with a specific immunity, such as the immunity resulting from a vaccination, alcoholics with these greatly increased antibody levels are often immunodeficient. These higher antibody levels may be due to abnormal regulation of the production of antibodies, or they may be a manifestation of autoimmunity.

Changes in the cell-mediated immunity of alcoholics include reduced response to tuberculin and fungal skin tests. Isolated lymphocytes taken from alcoholics also demonstrate a reduction in the immune response. Several recent reviews summarize studies on cell-mediated immunity in alcoholics (Cook 1995; MacGregor and Louria 1997; Paronetto 1993).

Alcoholics without liver disease typically have normal numbers of lymphocytes in their peripheral blood, while those with liver disease have a wide range of abnormalities. In patients with alcoholic hepatitis (an earlier stage of alcoholic liver disease), there is a mild reduction in lymphocyte numbers, with a return to normal levels after several weeks of recovery. However, patients with alcoholic cirrhosis (a later stage of alcoholic liver disease) may have lymphopenia, a severe reduction in lymphocyte numbers.

Abnormalities of immune function can be accompanied by changes in the percentages of different types, or subsets, of lymphocytes or by

changes in cell surface markers. Investigators have compared lymphocyte subsets in alcoholics and in nonalcoholic controls (Cook 1995). They have shown that, in alcoholics, the ratio of helper T-cells (designated CD4) to cytotoxic and suppressor T-cells (designated CD8) is normal or elevated. This finding is in sharp contrast to patients with AIDS, who have a greatly decreased CD4-to-CD8 ratio. Alcoholics also show changes in various molecules on the surface of T-cells that, taken together, may be considered a chronic activation of the T-cells. Recent studies have shown that T-cell activation is apparent for considerable periods of time after alcohol withdrawal (Laso et al. 1996, 1997).
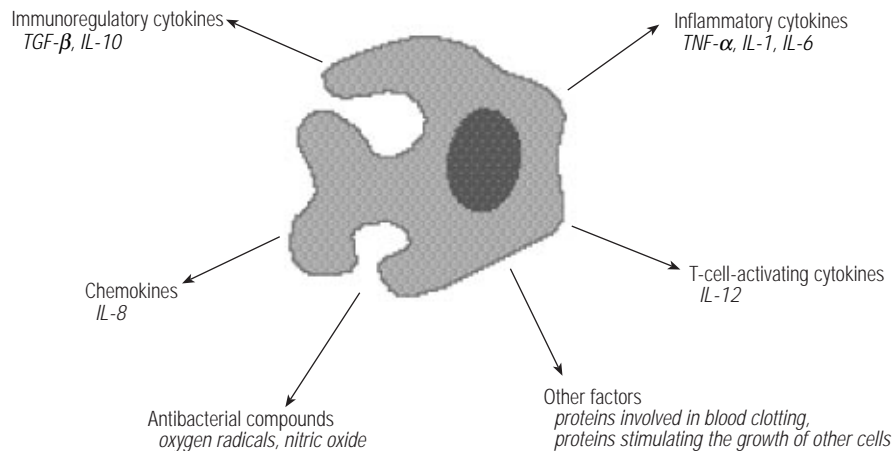
Alcoholics without liver disease tend to have normal numbers of B-cells, the antibody-producing lymphocytes. However, in patients with alcoholic liver disease, B-cells often are decreased in number, in spite of the fact that these cells produce abnormally large amounts of immunoglobulins. B-cells also show changes in their subset patterns (Cook et al. 1996; Laso et al. 1996), but these changes appear to be more short-lived than the T-cell changes (Laso et al. 1997). Together, the changes in both T-cells and B-cells suggest that there may be alterations in the interactions between the two types of cells that are important for understanding many of the defects of immune regulation in alcoholics.

Although results have been inconsistent, some investigators have reported that the NK cells have reduced functional activity in alcoholics (Charpentier et al. 1984). Recent work has shown that alcoholics without liver disease may have normal NK cell activity and numbers, but that some patients with alcoholic liver disease have greatly reduced NK cell numbers and loss of NK cell activity (Cook et al. 1997a; Kronfol et al. 1993). Interestingly, normal NK cells are mildly stimulated by overnight exposure to alcohol if activity is measured after alcohol removal (Li et al. 1997). This finding indicates that NK cell loss in alcoholics with liver disease is probably not a direct result of alcohol consumption but is an indirect consequence of other immune changes resulting from chronic alcohol exposure.

Neutrophils not only form one of the first lines of defense against invading bacteria, they also react to other stimuli, such as one's own tissues after damage by various agents. In alcoholic hepatitis, there often is an increase in the number of neutrophils in the blood, and microscopic examination of the liver shows infiltration of the liver by neutrophils. Since these cells typically release powerful enzymes that damage tissue, an abnormal number of neutrophils in the liver of alcoholics is one possible mechanism for liver damage. In some alcoholics with late-stage disease, neutrophil numbers in the blood may be significantly reduced, apparently because of bone marrow suppression, a situation that contributes to immunosuppression. Other neutrophil abnormalities associated with alcohol include reduction in the movement of neutrophils to sites of inflammation and decreased anti-bacterial activity (Cook et al. 1990).

Monocytes circulate in the blood and also have counterparts residing as fixed macrophages in many tissues, including the liver and lungs. These cells not only have the ability to engulf bacteria, they also produce chemicals that are toxic to bacteria. These and other functions can be altered by alcohol in cultured cells (Zuiable et al. 1992) and in the monocytes of alcoholic patients (Silvain et al. 1995), as can the substances derived from monocytes and macrophages (figure 1).

Cytokine balance is disrupted in alcoholic liver disease (McClain et al. 1993). The monocytes in the bloodstream and the fixed macrophages, such as the Kupffer cells in the liver, produce an excess of the proinflammatory cytokines IL-1, IL-6, and TNF in response to alcohol. These same cells are sensitive to stimulation by a lipopolysaccharide, known as LPS or endotoxin, a toxic substance produced in the cell walls of bacteria that commonly reside in the intestine. LPS is a powerful activator of many immune system cells. It can potentiate the effects of alcohol in activating macrophages, particularly the Kupffer cells. One result of this combined activation is to increase liver damage under experimental conditions. Since alcoholics can have increased

Figure 1: Monocyte- and macrophage-derived substances potentially affected by alcohol

Immunoregulatory cytokines
TGF-β, IL-10

Inflammatory cytokines
TNF-α, IL-1, IL-6

Chemokines
IL-8

T-cell-activating cytokines
IL-12

Antibacterial compounds
oxygen radicals, nitric oxide

Other factors
*proteins involved in blood clotting,
proteins stimulating the growth of other cells*

Monocytes and macrophages produce numerous substances that initiate and regulate inflammatory reactions; attract other immune cells (chemokines); stimulate T-cells; help in the elimination of pathogens, such as bacteria; and perform other functions throughout the body. Alcohol may interfere with the production and secretion of all these substances, thereby impairing the body's immune response.

IL, interleukin; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha.

Source: Szabo 1997.

levels of LPS in their blood, and their isolated monocytes may respond more strongly to LPS, it is possible that liver damage in alcoholics is accentuated by the interaction of alcohol and LPS (Schenker and Bay 1995). Stimulation by LPS causes the monocytes and macrophages to secrete more TNF (Schafer et al. 1995). Since TNF is toxic to many cells, excessive production of this cytokine contributes to cell death. Patients with acute alcoholic hepatitis have a poorer outcome if they have markedly elevated TNF levels in the blood, which seems to confirm this concept (Bird et al. 1990; Felver et al. 1990). Some researchers report that alcoholics produce lower than normal amounts of the anti-inflammatory cytokine IL-10, thus failing to inhibit the excessive production of pro-inflammatory cytokines such as TNF (Le Moine et al. 1995).

Experimental Models

In order to properly evaluate clinical observations and immune system changes found in human alcoholics, it is necessary to compare immune functions in animals and cell cultures. Mice and rats are fed alcohol in the diet or by direct infusion into the stomach so that levels of intake can be controlled carefully. The levels of alcohol mimic the approximate amount consumed by human alcoholics: 15 to 40 percent or more of total caloric intake. In some experiments, researchers administer larger amounts of alcohol in a single exposure to mimic the effect of human binge drinking. In most of these experiments, researchers then examine lymphocytes and other immune system cells for alterations in function, growth, and cell development. Other experimenters use isolated immune system cells grown in culture. After exposing the cells to alcohol for periods of up to a few days, they are able to

evaluate the direct effects of alcohol on specific functions. In addition to the research outlined below, several recent reviews describe other aspects of work in this area (Baker and Jerrells 1993; Jerrells and Sibley 1995; Jerrells et al. 1994).

Infectious Diseases

Animal models of infections in the presence or absence of alcohol have demonstrated a number of important findings (Jerrells et al. 1994). Bacterial pneumonia initiated by *Klebsiella* or *Streptococcus pneumoniae* causes increased mortality in alcohol-fed rats and mice (Lister et al. 1993*b*; Nelson et al. 1991). Several other infections are more severe or prolonged in these animals, including the systemic infection listeriosis and the gastrointestinal infections caused by *Salmonella* and by intestinal parasites such as *Nippostrongylus* (Jerrells et al. 1994).

Researchers have studied TB organisms both in mice and in cell cultures of macrophages, the cells that ordinarily provide a first line of defense against this organism. Alcohol exposure increased the number of TB organisms in both cases and caused changes in the TB organism that lessened the effectiveness of the macrophage response (Bermudez et al. 1992, 1994). Some investigators have produced limited data suggesting that, in contrast to the worsening of TB infections after standard chronic alcohol exposures, low-dose alcohol exposure in experimental animals may actually improve the response to the TB organism (Mendenhall et al. 1997*b*). Other factors that may be involved in these alcohol-TB interactions have been reviewed recently (Nelson et al. 1995).

Immune System Cells

Cells of the Lymphoid Organs. Both chronic and acute alcohol administration can produce loss of lymphocytes from the thymus, spleen, and lymph nodes of experimental animals (Ewald 1989; Ewald and Shao 1993; Jerrells et al. 1994; Pruett et al. 1994). The cell types lost include B-cells, NK cells, and thymocytes, which are the developing T-cells in the thymus. The mechanisms of these cell losses appear to include a form of cell suicide known as apoptosis (programmed cell death). This phenomenon is discussed in detail in the section "Alcohol-Induced Liver Injury" earlier in this chapter. Under normal conditions, apoptosis helps to maintain the balance of cell numbers throughout the body. It is currently thought that alcohol may affect this process by disturbing the balance between cell increase through cell division and cell loss through apoptosis. One possible alcohol-induced disturbance in the thymus would be a selective apoptosis that would fail to delete self-reactive cells, resulting in a predisposition to autoimmunity. Recent research tends to discount this possibility (Livant et al. 1997). However, several investigators are actively pursuing the study of alcohol-induced apoptosis in other organs and cells, and new insights are anticipated.

T-Cells. Experimenters have exposed isolated lymphocytes of alcohol-fed animals to various agents in order to evaluate T-cell responsiveness to these agents. Results from one study indicated that stimulation by nonspecific agents or stimulation in the presence of mixed-cell populations caused a reduced response by the T-cells of alcohol-fed animals (Baker and Jerrells 1993). However, there has been some doubt as to whether the reduction was actually due to a T-cell alteration by alcohol. More recent work has used stimulation of T-cells by antibody to the T-cell receptors, mimicking the stimulation by antigen specific for the receptor. These studies have suggested that the inhibition produced by alcohol consumption may indeed be due, at least in part, to an alcohol-associated T-cell defect (Domiati-Saad and Jerrells 1993). In addition to reductions in T-cell proliferation, there appear to be alterations in the amount or pattern of cytokine production by T-cells in alcohol-fed animals.

Monocytes. Researchers have shown that exposure of cultured normal human monocytes to alcohol concentrations similar to those seen in binge drinkers reduces the ability of these monocytes to present antigen to T-cells (Szabo et al. 1993). (It is necessary for an "antigen-presenting" cell to process and display antigen in a way that the

T-cell will recognize it.) Researchers attributed this reduction to an alcohol-induced imbalance of cytokines. Experiments with cultured cells from alcohol-fed animals also showed a reduction in antigen presentation (Mikszta et al. 1995). Other animal research found genetic variation in the degree of alcohol-induced reduction in T-cell responses (Schodde et al. 1996). When cells were exposed to alcohol after antigen presentation, the effectiveness of the T-cell response was not diminished (Waltenbaugh and Peterson 1997). The reduction in cell-mediated immunity so commonly seen in chronic alcoholics thus appears to be partly due to the loss of an early step in antigen presentation. This could be a result of a functional change in monocytes and/or a change in T-cell-monocyte interactions.

Natural Killer Cells. Some alcoholics, especially those with cirrhosis, may have considerably reduced NK cell activity as measured in their isolated lymphocytes (Charpentier et al. 1984). Studies in alcohol-fed mice and rats have generally shown that the effect of alcohol on NK cell activity depends greatly on such factors as nutritional state, specific genetic strain, age, exercise, and amount and timing of alcohol administration (Cook et al. 1997*a*; Li et al. 1997). Nevertheless, chronic alcohol ingestion clearly inhibits NK cell activity in some mouse strains (Gallucci et al. 1994). A binge-equivalent single administration also can temporarily reduce both NK cell numbers and activity (Wu et al. 1994).

Indirect clinical evidence implicates NK cells in immune system protection from various cancers. Since alcohol can reduce NK cell numbers and activity, several studies have compared the spread of experimental tumors in animals both with and without continuous alcohol exposure. Some experiments suggested enhancement of tumor spread by alcohol, presumably mediated by alcohol-induced NK cell suppression (Yirmiya et al. 1992). Other studies, using a different tumor model, reported suppression of tumor spread (Meadows et al. 1993). Some data indicate that both the exact site of the tumor

and previous exposure of the cells to alcohol are important in predicting whether alcohol will accelerate or retard tumor spread (Blank and Meadows 1996).

Neutrophils. More than half a century ago, an investigator observed that alcohol prevented the neutrophils of intoxicated rabbits from reaching the skin and lungs in response to the administration of pneumococcal bacteria (Pickrell 1938). Later investigators confirmed that alcohol inhibited neutrophil migration in humans (Brayton et al. 1970; Gluckman and MacGregor 1978) and in experimental animals (Astry et al. 1983; Avaria et al. 1981; Nelson et al. 1991).

A critical factor in the migration of immune cells across capillary walls is the presence of certain proteins, known as adhesion proteins, on the cell surface (Gallatin et al. 1983; Lewinsohn et al. 1987). Some researchers have reported that alcohol reduces the expression of adhesion molecules, with the result that fewer immune cells arrive at sites of infection (MacGregor et al. 1988; Zhang et al. 1997*b*). On the other hand, other researchers have reported increases in the levels of adhesion molecules in human alcoholics (Cook et al. 1994; Santos-Perez et al. 1996) and in animals (Bautista 1995, 1997; Nanji et al. 1995*b*). These increases could be a partial explanation for the infiltration of neutrophils into the liver that is observed in alcoholic hepatitis. A complicating factor is the observation that the migration of neutrophils to infection sites is altered after acute alcohol ingestion similar to binge drinking (Nelson et al. 1991) but not after chronic alcohol exposure (Lister et al. 1993*a*). This observation suggests that chronic exposure may lead to adaptation in adhesion molecules, a situation that makes predictions extremely difficult.

Since chronic alcohol exposure in experimental models may not reduce neutrophil migration to the lung, researchers evaluated the effectiveness of other neutrophil functions, such as phagocytosis and killing of pneumococcal bacteria. Experiments with alcohol-fed rats showed that their neutrophils phagocytosed bacteria efficiently but

did not kill all strains of pneumococcal bacteria with normal effectiveness (Jareo et al. 1995, 1996). It is interesting that one study of alcohol-fed rats reported changes in pulmonary surfactant, a lung secretion, that resulted in a lessening of antibacterial activity (Rubins et al. 1996).

Cytokines

Acute exposure to alcohol in LPS-stimulated normal rats can produce rapid changes in the production of several cytokines (Nelson et al. 1995). Experiments with isolated human monocytes show the same effects (Mandrekar et al. 1996; Szabo et al. 1992, 1996*a,b*; Verma et al. 1993). The changes reported include increases in some cytokines and decreases in others. These changes have important implications for immunity because cellular immune reactions are dependent on different cytokines for their initiation and continuation. Other experiments have shown that changes in cytokine balance in alcoholics may be due to a reduction in a process known as endocytosis, in which the cytokine is taken up by the cells and degraded (Deaciuc et al. 1996; Tuma et al. 1996*b*).

Animal research supports the concept of increased levels of proinflammatory cytokine production after exposure to alcohol. Animal studies also confirm the additive effects of LPS and alcohol in producing liver injury (Kamimura and Tsukamoto 1995; Pennington et al. 1997). In the lung, however, the LPS-stimulated secretion of proinflammatory cytokines actually may be reduced in alcohol-fed animals (Standiford and Danforth 1997) and in human alcoholics (Gosset et al. 1995). This reduction in cytokines could increase susceptibility to pneumonia. Consistent with this finding, researchers have reported a loss of TNF receptors on lung macrophages (D'Souza et al. 1994).

The cytokine IL-8 causes an increase in the number and activity of neutrophils. IL-8 is elevated in patients with alcoholic hepatitis, and this elevation may be one mechanism for the increased infiltration of the liver by neutrophils in this disease (Bird 1994; Hill et al. 1993; Huang et al. 1996). Recent work with rats indicates that the stimulation of IL-8 production in alcoholics may be indirect, involving interactions of alcohol metabolism, liver cells, and Kupffer cells (Maher 1995).

Current Directions

In the past several years, research in immunology has shown that there is a dramatic degree of interaction and mutual regulation among the different types of immune system cells. The insights from this work have led to many new avenues for investigation.

TH1/TH2 Immunity

One of the most fascinating and useful developments in immunology in the past several years has been the description of polarized responses of the immune system according to the offending agent, the type of immune cell encountered, and the cytokine environment in which the response occurs (Fitch et al. 1993; Medzhitov and Janeway 1997; O'Garra and Murphy 1994; Romagnani 1995). As noted earlier, the cells of the immune system respond to infectious agents along two broad pathways—cell-mediated immunity and humoral immunity. Within these pathways are further distinctions based on the type of infectious agent and the cytokine environment that stimulates the response most strongly.

TH1 (referring to a subset of T-helper cells) responses are predominantly cell mediated and are stimulated most strongly by the cytokines IL-12 and interferon gamma (IFN-γ). TH2 (an alternate subset of T-helper cells) responses are predominantly humoral, or antibody mediated, and are stimulated most effectively by the cytokines interleukin-4 (IL-4), interleukin-5 (IL-5), and IL-10. If the TH1/TH2 balance is skewed too far in one direction, immunologic disease may result. Autoimmunity is often associated with TH1 reactions, while immunodeficiency and allergies may be polarized toward a TH2 response (Romagnani 1995).

The responses tend to be mutually inhibitory. For example, the maturation of T-cells in a TH2 environment results in a preponderance

of TH2-type T-cells, with inhibition of TH1 development. It is of great interest to determine what factors in the infectious agent or in the environment influence the direction of the initial immune response toward TH1 or TH2. Current evidence points toward monocytes and other antigen-presenting cells as critical in the initial interpretation of the offending agent and the production of the cytokines that will stimulate either a TH1 or TH2 response (Medzhitov and Janeway 1997). This innate, first-responding component of the immune system is distinguished from the adaptive immune system consisting of T-cells and B-cells. This adaptive system produces cells that respond to specific antigens and that confer specific long-term immunity to those antigens.

The immune abnormalities seen with alcohol abuse, including elevated immunoglobulin levels and immunodeficiency, may be the result of polarization toward excess TH2 function (Cohen 1995). However, the TH1/TH2 balance in alcoholics with late-stage cirrhosis may be different from that of alcoholics with early acute alcoholic hepatitis. It is important to determine whether TH1/TH2 imbalance is caused by acute or chronic alcohol abuse and, if so, whether this imbalance could account for immune abnormalities.

Results of recent work with cultured normal human monocytes acutely exposed to alcohol indicate an increase in IL-10 and a decrease in IL-12 (Girouard et al. 1998), which would shift the TH1/TH2 balance toward TH2. Another recent study showed that the cells of alcohol-fed mice tend to shift toward a TH2 response, with a decrease in TH1 response (Peterson et al. 1998*b*). This second report offers a possible mechanism for the shift. Glutathione, a protective antioxidant, is known to be depleted by heavy alcohol consumption; in the cell cultures used for this research, reduction of glutathione also caused a shift toward TH2 cytokine production (Peterson et al. 1998*a*). The observations reported by these two groups represent an exciting new direction for analysis of the immunologic abnormalities caused by alcohol abuse. TH1/TH2 balance

must now be evaluated in the human alcoholic whose innate and adaptive immune systems have had many years of high-level exposure to alcohol.

Molecular Regulation

Transcriptional Control. When an agent that influences cell behavior, such as an antigen stimulating an immune response, interacts with the cell, its influence on the cell occurs through an elaborate sequence of molecular events. The first such event is binding to a cell surface receptor. That receptor then conveys a signal to the cell's interior. This signal is interpreted in the cell's cytoplasm, and a new signal is transmitted to the nucleus, where interaction with cellular DNA occurs. The DNA transcribes the message to a strand of ribonucleic acid (RNA), which then directs the synthesis of new proteins, such as cytokines. These proteins are transported out of the cell, where they influence the original agent or other cells in the vicinity.

Although there are no specific cell receptors for alcohol, alcohol does influence this sequence of events in several ways. Both potassium and calcium ion concentrations change rapidly in the cell's interior during various types of cell activation events, and they often are measured as indirect indicators of changes within the cell. After short-term alcohol exposure, potassium conductance is increased (potassium channels in the cell membrane are opened) in T-cells (Oleson et al. 1993), and intracellular calcium concentrations are shifted in neutrophils (Nilsson et al. 1992; Patel et al. 1996) and in Kupffer cells (Hijioka et al. 1993). Although there has been little research on alcohol's direct effects on specific signaling pathways in immune system cells, studies of liver cells and tumor cells show that alcohol can cause alterations in receptor molecules and other molecules in the signal cascade leading to cell activation (Saso et al. 1996; Thurston and Shukla 1992; Zeldin et al. 1996). It is clear from these and other results that alcohol alters the molecular mechanisms that control cell responses to normal stimuli. An understanding of the consequences of these changes will require further study.

One of the cytoplasmic elements involved in the activation of cellular responses is a transcription factor called nuclear factor kappa B (NFκB). This molecular complex is activated by signaling events. It is then transported to the nucleus, where it binds to DNA and initiates the synthesis of RNA. Researchers have examined the effect of acute alcohol exposure on this process in Kupffer cells of experimental animals (Fox et al. 1996) and in normal human monocytes (Mandrekar et al. 1997). Both studies reported disturbances of LPS-induced NFκB activation. The study of human cells reported that alcohol disturbed the NFκB complex in such a way that the signal to the nucleus was inhibitory rather than stimulatory (Mandrekar et al. 1997).

Mediators of Inflammation. Cells of the innate immune system produce reactive oxygen species (ROS), toxic substances that kill bacteria and cause inflammation. These species include nitric oxide (NO), hydrogen peroxide, and other highly reactive chemicals. Since the cells that produce ROS are ubiquitous, abnormally increased or persistent activation of the pathways leading to production of these chemicals could cause tissue destruction and inflammation.

Studies of liver injury find that alcohol-fed animals have higher levels of ROS resulting from increased NO production after LPS stimulation (Chamulitrat and Spitzer 1996). The effect of NO in causing liver damage may depend on the type of liver cell producing the increase (Nanji et al. 1995*a*). Protective mechanisms within the liver are themselves affected by alcohol and also are influenced by cytokines whose balance, in turn, is affected by alcohol (Perera et al. 1995). These and other recent studies (Higuchi et al. 1996) have emphasized the complexity of interactions between factors regulating the immune system and tissue injury caused by ROS produced by the immune system.

If production of ROS were inhibited by alcohol, the effectiveness of the immune system cells in killing bacteria and other infectious agents would be reduced, leading to immunodeficiency. In rats, several days of alcohol feeding caused a reduction

in the release of ROS from their cultured neutrophils when challenged by pneumococcal bacteria (Jareo et al. 1996). Acute administration of alcohol to rats reduced NO production by isolated lung macrophages after challenge with TB organisms (Greenberg et al. 1995). Further work with the regulatory enzyme for NO production showed that its induction by LPS is suppressed by both acute and chronic alcohol exposure. However, other ROS may differ in their response to acute versus chronic exposure (D'Souza et al. 1996). It is clear that investigation of the production of NO and other ROS has significant potential for contributing to knowledge of alcohol-induced tissue injury and immunodeficiency.

Acetaldehyde-Protein Adducts. Acetaldehyde, the first product of alcohol metabolism, is reactive and combines chemically with proteins in the cells or blood of the person or animal consuming the alcohol (Crossley et al. 1986; Hoerner et al. 1986; Israel et al. 1986; Tuma et al. 1987). These chemical combinations are called adducts. The development of autoimmunity after alcohol exposure may be a result of the formation of these acetaldehyde-protein adducts. Many investigators have found antibodies to these adducts produced after chronic exposure to alcohol. Research has shown that new antigens may persist for up to 30 days after alcohol exposure in animals (Anthony et al. 1983), providing ample exposure time of the adducts to the immune system.

Later studies have found not only that acetaldehyde forms adducts to nonprotein molecules but that nonacetaldehyde products of alcohol metabolism form adducts to cellular or blood components (Chang et al. 1997; Clot et al. 1995; Trudell et al. 1991). For example, the alcohol-induced cytochrome P450 2E1 readily forms adducts with hydroxyethyl. More than 85 percent of alcoholics with cirrhosis have antibodies that react to this adduct (Clot et al. 1996). Further experimentation with this adduct, using rat liver cells and IgG antibodies from patients with alcoholic liver disease, resulted in an antibody-dependent cytotoxic effect in the cells (Clot et al. 1997). This finding clearly

demonstrated the potential cellular toxicity of the antibodies to this adduct.

There have been major efforts to determine the mechanisms of formation of acetaldehyde-protein adducts and to establish their clinical significance. One study of persons who drank heavily found high levels of IgA and IgM antibodies to acetaldehyde-albumin adducts, and that the IgA antibodies were correlated with alcohol intake (Worrall et al. 1996). A study of 140 alcohol drinkers and nondrinking controls found anti-acetaldehyde-adduct antibodies of each immunoglobulin class in these subjects (Viitala et al. 1997). The levels of antibodies were higher in drinkers than nondrinkers, including those with nonalcoholic liver disease, and antibody levels were positively correlated with several indicators of liver disease severity.

Determination of the immunologic relevance of acetaldehyde-protein adducts produced in cell cultures has been complicated by the fact that various products are formed depending upon the chemical environment (Klassen et al. 1994; Thiele et al. 1994). Therefore, antibodies with specificity for adducts prepared under different experimental conditions were developed for further analysis of the effects of these adducts in alcohol-fed animals. Researchers recently found that another aldehyde generated during alcohol metabolism, malondialdehyde, could react with coexisting acetaldehyde (Tuma et al. 1996*a*). The mixed adduct is called MAA. Antibodies specific for MAA did not cross-react with known acetaldehyde-only or malondialdehyde-only adducts. These antibodies were used to show that alcohol-fed rats have significant amounts of this mixed adduct in their livers.

This work with adducts and antibodies to them, with their clear potential for cellular cytotoxicity, represents exciting progress in understanding how alcohol may produce autoimmunity and tissue damage. It provides one possible explanation for the increasing severity of alcoholic hepatitis in successive episodes and may help explain the progressive damage that occurs for some time after alcohol withdrawal in many patients.

Therapeutic Measures

Alcohol has a great array of effects at the molecular, cellular, and organ levels. These effects may be produced by alcohol that is consumed in acute, bingelike episodes or in chronic excess. With so many variables to consider, therapeutic approaches must be based on a specific goal. Researchers must determine whether the immediate problem is restoration of TH1/TH2 balance, reduction of an autoimmune process, or repair of scarring produced by the autoimmune process. There are many possible approaches to preventing acute alcoholic liver injury (McClain et al. 1993), and the same principles apply to manipulations of the immune system. Some proposed therapies include administration of such substances as antibodies against endotoxin (LPS) or against specific cytokines, soluble cytokine receptor molecules that would absorb excess cytokines, cytokine receptor antagonists, drugs that block either cytokine production or specific responses, adhesion molecule antagonists, and drugs that have a widespread effect (such as improvement of gut integrity).

Most investigators have dealt with acute problems such as alcoholic hepatitis or pneumonia. In studies of pneumonia, several groups have used granulocyte colony-stimulating factor (GCSF) to improve neutrophil number and function (Nelson 1994). GCSF is a neutrophil-specific growth factor that stimulates the growth of neutrophils and enhances their activity. In alcoholic rats infected with *Klebsiella pneumoniae,* GCSF improved neutrophil influx and survival (Nelson et al. 1991). GCSF also increased migration of neutrophils into the lungs of alcohol-fed rats with pneumococcal pneumonia or after administration of LPS (Lister et al. 1993*a*; Preheim et al. 1996), but it did not always improve survival. Consistent with increased neutrophil migration to the lungs, adhesion molecule expression was improved in neutrophils after GCSF treatment (Zhang et al. 1997*a*). Although experimental results are encouraging, there have been few attempts at GCSF treatment in human alcoholics (Grimsley 1995).

If the TH1/TH2 balance is proven to be significant in immunologic disturbances of alcohol abusers, methods of correcting the imbalance will need to be found. Recent work with rats has shown that cell-mediated immunity (TH1) is reduced by 10 days of alcohol feeding but that certain TH2 functions are not changed. Administration of IL-12 restored both the TH1 functions and the ability of isolated lymphocytes to make IFN-γ, a critical TH1 cytokine (Peterson et al. 1998*b*). Other investigators, using a more direct route to TH1 enhancement, administered the IFN-γ by means of an experimentally altered virus, called an adenoviral vector, introduced into the trachea (Kolls et al. 1998). This procedure resulted in enhanced IFN-γ production by the lung, improved TNF responses after stimulation with LPS, increased recruitment of neutrophils into the lung, and reduced bacterial survival. It also reversed the effects of acute alcohol administration on these measures.

Another recent therapeutic approach involves attempts to improve overall protein balance and metabolic status in malnourished alcohol-fed rats. Hormonal therapy with insulin-like growth factor and growth hormone was successful in improving nutritional state, and it also improved some, but not all, measures of immune function (Mendenhall et al. 1997*a*).

These are exciting new approaches to specific types of therapy for the alcohol-damaged immune system. New discoveries in this rapidly developing field will lead to additional therapeutic measures based on specific or general immunotherapy.

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Glossary

Adaptive immunity: Also called adaptive immunity. Immunity that is activated after the body is exposed to a pathogen. The most important cells in acquired immunity are the T-cells and B-cells. See innate immunity.

Adduct: The product resulting from the attachment of one type of molecule to another. For example, an acetaldehyde molecule may attach to a protein molecule, forming an acetaldehyde-protein adduct.

Adenoviral vector: An altered adenovirus that can still invade cells but does not have the ability to produce disease. Genes purposely introduced into its structure are carried into the host cells.

Adhesion molecules: Several classes of protein molecules on the surface of cells and membranes that can bind to molecules on another surface, thus binding the surfaces together.

Antibody: A protein molecule produced by B-cells in response to an antigen. Its structural specificity allows it to bind the antigen.

Antigen: A molecule interpreted by the immune system as foreign (such as a surface component of a bacterium) and that elicits specific antibody production.

Antioxidant: A protective molecule that neutralizes reactive oxygen species.

Apoptosis: A process of cell "suicide" elicited by some specific signal such as a cytokine. It is a part of normal cell physiology necessary for maintaining a balance between cell growth and loss. In the immune system, apoptosis also rids the body of self-reactive (autoimmune) cells.

ATP: Adenosine triphosphate. An essential molecule involved in the cell's energy-consuming metabolic processes. It is necessary for normal cell function.

Autoantibody: An antibody that reacts with a self-antigen, which can be a normal or altered cell or tissue of the body.

Autoimmune reactions: Immune responses directed at the body's own cells and tissues. These inappropriate reactions can result in autoimmune diseases and disorders.

B-cell: A type of lymphocyte that produces antibody. B-cells are the primary source of humoral immunity.

CD4 and CD8 T-cells: CD4 T-cells are helper T-cells; CD8 T-cells are cytotoxic and suppressor T-cells. Changes in the ratio of CD4 to CD8 cells are considered to be indicators of abnormalities in immune function.

Cell-mediated immunity: Immunity provided by the direct action of immune system cells, primarily the T-cells. See humoral immunity.

Chemoattractant: A substance that attracts migratory cells, such as neutrophils, to a specific site.

Choline: A substance that prevents the deposition of fat in the liver. A deficiency of choline causes severe fatty deposits.

Collagen: The major protein constituent of connective tissue. It is the protein that forms scar tissue.

Cytochrome P450 2E1: An enzyme that metabolizes alcohol and causes the generation of reactive oxygen species.

Cytokines: Small molecules that act as chemical messengers, regulating cellular interactions and functions. They play an important role in cell-to-cell communication during normal metabolism and are the primary chemical messengers during periods of inflammation or infection.

DLPC: Dilinoleoylphosphatidylcholine. A protective substance that acts to prevent fibrosis and appears to have antioxidant properties.

Endothelial cells: Cells that line the interior of blood vessels.

Endotoxin: A lipopolysaccharide (LPS). A toxic molecule found in the cell wall of certain bacteria.

Fas: Also called CD95 or APO-1/Fas. A specific receptor, or docking site on a cell, that reacts with a corresponding molecule, Fas ligand. The joining of Fas with Fas ligand initiates chemical processes within the cell that can lead to cell death by apoptosis.

Fatty liver (steatohepatitis): Deposition of fat in the liver.

Fibrosis: Deposition of collagen in the form of scar tissue. It can lead to cirrhosis.

Glutathione: An antioxidant found in mitochondria.

Hepatitis: An inflammation of the liver with associated pain, fever, and jaundice. It may be induced by alcohol (alcoholic hepatitis) or by a virus, such as hepatitis B or hepatitis C.

Hepatocytes: The main functional cells of the liver. They process and store nutrients, remove toxins from the blood, and secrete bile, which is involved in the digestion of fats.

Humoral immunity: Immunity conferred by antibodies that circulate in the blood and lymph. Antibodies are produced by B-cells. See cell-mediated immunity.

IFN-γ: Interferon gamma. A cytokine that induces protection against viral infection and stimulates macrophages and neutrophils.

IL-1: Interleukin-1. A cytokine that induces inflammation, stimulates proliferation of helper T-cells, and promotes B-cell growth and differentiation.

IL-4: Interleukin-4. A cytokine that stimulates T-cell growth, induces B-cell activation and growth, and modulates antibody production by B-cells.

IL-6: Interleukin-6. A cytokine that induces inflammation and promotes the maturation of B-cells into plasma cells.

IL-8: Interleukin-8. A cytokine that attracts and stimulates neutrophils.

IL-10: Interleukin-10. A protective cytokine with anti-inflammatory effects. It inhibits T-cell proliferation, reduces the production of inflammatory cytokines, and promotes B-cell proliferation and antibody secretion.

IL-12: Interleukin-12. A cytokine that activates natural killer cells, activates a subtype of T-cell, and induces the cell-mediated (TH1) immune response.

Immunodeficiency: A condition in which some component of the immune system functions at too low a level to provide normal protection.

Immunoglobulins: Several classes of antibody proteins produced by B-cells. The major classes are immunoglobulins A, G, and M (IgA, IgG, and IgM).

Innate immunity: Immunity that does not require prior exposure to an antigen. The main components of innate immunity are the phagocytes, which attack any invading organism regardless of prior exposure, and the natural killer cells. See acquired immunity.

Interferon: A substance produced by cells that have been infected with a virus. It moves to noninfected cells, where it confers resistance to that virus.

Kupffer cells: Phagocytic cells resident in the liver. They engulf and destroy invading substances and secrete cytokines, such as tumor necrosis factor alpha.

Leptin: A hormone that controls appetite.

Lipid peroxidation: A reaction between reactive oxygen species and components of cell membranes. It is a destructive process that may degrade cell membranes and impair cell function.

LPS: Lipopolysaccharide. See endotoxin.

Lymphocyte: A class of immune cell that includes T-cells, B-cells, and natural killer cells.

Macrophage: A phagocytic cell found in the tissues, such as the liver (Kupffer cells) and lung. It develops from a monocyte.

MAT: Methionine adenosyltransferase. An enzyme involved in the production of *S*-adenosyl-L-methionine (SAM).

Methionine: An amino acid that is essential in the diet and necessary for normal metabolism.

Mitochondria: Small bodies within the cell, each enclosed in its own membrane. They generate energy for the cell's metabolic processes.

Monocyte: A phagocyte that circulates in the blood stream. Monocytes may migrate into the tissues, where they develop into macrophages.

mRNA: Messenger ribonucleic acid. A complementary copy of a gene in the DNA. It encodes proteins and participates in protein synthesis.

NAPQI: *N*-acetyl-*p*-benzoquinonimine. A highly reactive product of acetaminophen metabolism. If it is not bound by the antioxidant glutathione, it causes serious cell damage.

NASH: Nonalcoholic steatohepatitis, fatty liver not related to alcohol consumption. It is characterized by inflammation, fibrosis, and cirrhosis.

Natural killer (NK) cells: A type of lymphocyte that attacks virus-infected or cancerous cells without a requirement for previous exposure.

Necrosis: A type of cell death whereby the cell swells and breaks open, releasing its contents.

Neutrophil: A phagocytic cell that circulates in the blood and attacks bacteria without a requirement for previous exposure. Neutrophils react to chemoattractants such as interleukin-8 by moving to the site of inflammation, where they adhere to cell surfaces. When present in excess, they damage cells by releasing toxic metabolites.

NFκB: Nuclear factor kappa B. An oxidative stress-sensitive transcription factor involved in the production of certain cytokines. It is a regulatory complex of molecules that lies in the cell cytoplasm until activated by signals from the cell exterior. It then moves to the nucleus to initiate specific RNA synthesis.

Oxidative stress: A condition caused by an excess of reactive oxygen species and/or a deficiency of antioxidants. This imbalance causes cell damage and may end in cell death.

Phagocyte: A cell that engulfs and destroys bacteria and other foreign substances. This process is called phagocytosis. The phagocytes include monocytes, macrophages, and neutrophils.

Plasma cell: A large cell that develops from a B-cell after it encounters an antigen. The plasma cells produce large numbers of antibodies to that specific antigen.

PPC: Polyenylphosphatidylcholine. A substance extracted from soybeans. It acts to prevent the development of alcohol-induced fibrosis.

Prostaglandin: One of a family of compounds that affect various physiologic functions. Certain prostaglandins have protective effects on liver cells. Other prostaglandins affect other bodily functions, including smooth muscle contraction, blood pressure, body temperature, and blood clotting.

Reactive oxygen species (ROS): Also called free radicals. Highly reactive molecular fragments that are released during metabolic processes. If not promptly removed by antioxidants, they can interact with cell components and cause serious damage, such as lipid peroxidation.

Receptor: A specific docking site on a cell that connects with a corresponding molecule.

SAM: *S*-adenosyl-L-methionine. A precursor of glutathione. It has a beneficial effect on mitochondrial membranes, allowing normal transport of glutathione through the membranes.

Steatohepatitis: Fatty liver.

Stellate cells: Fat-storing cells in the liver. They produce collagen, which leads to fibrosis.

T-cell: A type of lymphocyte that produces cell-mediated immunity. Helper T-cells produce and secrete cytokines that stimulate the activity of other immune cells. Cytotoxic T-cells recognize antigens on the surface of virus-infected or transplanted cells and destroy those cells. Suppressor T-cells inhibit other immune responses, thereby preventing overreaction of the immune system.

T-cell receptor: A characteristic signaling molecule on the surface of T-cells. It has high molecular specificity for antigens.

TGF-β: Transforming growth factor beta. A cytokine that induces stellate cells to synthesize collagen. It can cause direct cell damage and increase liver inflammation.

TH1: A type of immune response that is primarily cell mediated.

TH2: A type of immune response that is primarily humoral, or antibody mediated.

Thymocyte: A cell that migrates from the bone marrow to the thymus, a lymphoid organ. In the thymus, the thymocytes develop into T-cells having the ability to recognize and respond to antigen.

TNF (TNF-α): Tumor necrosis factor alpha. A cytokine produced mainly in Kupffer cells. It induces inflammation, stimulates neutrophils, and induces the production of other cytokines, including more TNF.

Transcription: The enzymatic process by which the code for a specific gene in the DNA is transcribed into the same code in a strand of messenger RNA, which will later direct protein synthesis.